

# Huntington's disease in Chinese: a hypothesis of its origin

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## Abstract

**The period prevalence (1984-91) of Huntington's disease (HD) in Hong Kong Chinese was 3.7 per million population. HD patients in Mainland China and Hong Kong showed similar hereditary pattern, clinical and pathological features as in the West. Chinese HD patients were male predominant with a younger age of onset and death. Their ancestral origin could be traced mostly to the coastal provinces of China. It is proposed that Chinese HD patients may have a European origin and share the same gene pool as their white counterparts.**

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The prevalence of HD in the West varies from 40-100 per million population with pockets of high density in some areas.<sup>1</sup> The origin of most cases in white populations can be traced to their ancestors who left England, France or the Netherlands in the 17th or 19th century.<sup>2-6</sup> The European origin of the HD in Australia, North and South America is undisputed.<sup>7</sup>

Literature on HD in the East is limited due to the relative rarity of the disease. In Japan, the first case was reported in 1935 by Kishimoto. The prevalence was 4/10<sup>6</sup> in the Aichi province, approximately one-tenth that of the Western countries.<sup>8</sup> The negative assortive marriage, incomplete penetrance (penetrance estimated to be 0.94) and above all low detection rate were reasons cited as an explanation of the low prevalence rate. More recent data suggested an even lower figure of 1.1/10<sup>6</sup> in the Ibaraki Prefecture.<sup>9</sup> The annual death rate from HD in Japan was estimated to be 0.15 per million population, again about one-tenth of the figure in the West.<sup>1-10</sup> Isolated cases were also reported from the Indian subcontinent but the lack of systematic survey precluded reliable estimation of the prevalence.<sup>11-13</sup>

The data on Chinese are even more scarce and have been published mainly in the Chinese literature. In Hong Kong, only two reports with seven cases have been published so far<sup>14-15</sup> and the prevalence has not been studied. This paper reviews all reports on HD patients from Mainland China and Hong Kong, and discusses a hypothesis for the origin of HD in Chinese.

## Methods

Reports of HD in Chinese published in major

neurology and psychiatry journals of Mainland China and the West from 1950-90 were reviewed. Only index cases were included. A systematic survey of HD was conducted at all major neurology and psychiatry units in Hong Kong. Public announcement through newsletters to all local doctors was followed by personal contact. Each patient was examined by a neurologist and a psychiatrist. The diagnosis of HD was based on the presence of a positive family history, insidious, progressive chorea and disorder of voluntary movement, cognition, and often psychiatric disturbance.<sup>16</sup> Laboratory investigations were performed to aid the diagnosis. These included blood counts and smear, serum copper and caeruloplasmin, blood biochemistry, EEG and CT of brain. Caudate atrophy on CT supported the diagnosis. Conditions which may mimic HD including Wilson's disease, senile chorea, benign hereditary chorea and neuroacanthocytosis were therefore excluded. The hereditary pattern, ancestral origin, clinical and pathological features were reviewed. The sex distribution, mode of parental transmission and age of onset were analysed with chi-square and Wilcoxon tests.

## Results

Up to 1990, a total of 69 index patients have been reported in Mainland China and Hong Kong.<sup>14-17-30</sup> The recent survey in Hong Kong collected another 20 cases, making a total of 89. Without an epidemiological investigation, we could not discover the prevalence of HD in Mainland China. In Hong Kong, 20 Chinese HD patients from 11 families were identified between 1984-91. As the average Chinese population during this period was 5.44 million, the period prevalence was 3.7 per 10<sup>6</sup>. Six patients had died by 1991. There were therefore 14 patients in the 5.55 millions Chinese population of Hong Kong at 1991, hence the point prevalence of 2.5 per 10<sup>6</sup>.

The first HD patients in Mainland China and Hong Kong were reported by Wang<sup>18</sup> in 1959 and Singer<sup>15</sup> in 1962 respectively. There were all together 63 males and 26 females reported with a ratio of 2.42:1 (table). The male predominance was statistically significant,  $X^2 = 15.3$ ,  $df = 1$ ,  $p < 0.001$  (chi-square test). Of the 89 index patients who came from 63 families, a positive family history was obtained in 72. Paternal transmission was found in 50 patients (69.4%) and maternal in 22 (30.5%) with statistically significant difference,  $X^2 = 10.89$ ,  $df = 1$ ,  $p < 0.001$  (chi-

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Table Huntington's disease in mainland China and Hong Kong

Author		Number of Index cases	Sex M:F	Transmission Pat:Mat	Number of Pedigrees
<b>Mainland China</b>					
Wang	1959	2	1:1	1:0	2
Yin	1963	1	0:1	0:1	1
Liu <i>et al</i>	1980	2	1:1	2:0	2
Li and Luan	1980	4	2:2	3:1	1
Li	1981	6	4:2	3:3	3
Liu <i>et al</i>	1982	8	7:1	3:3	8
Shen <i>et al</i>	1983	3	3:0	0:1	3
Li <i>et al</i>	1985	29	21:8	15:7	24
Chen <i>et al</i>	1987	2	1:1	2:0	1
Ha <i>et al</i>	1988	2	1:1	2:0	1
Dai and Gao	1988	4	3:1	NA	4
Zhao <i>et al</i>	1989	2	2:0	2:0	1
Shao <i>et al</i>	1989	1	1:0	1:0	1
Total		66	47:19	34:16	52
<b>Hong Kong</b>					
Singer	1962	3	1:2	2:1	1
Present series	1991	20	15:5	14:5	10
<b>Mainland China and Hong Kong</b>					
		89	63:26	50:22	63

NA = not available

Pat = paternal

Mat = maternal

square test). The mode of inheritance was autosomal dominant. The most distant family history could be traced back five generations.<sup>31</sup>

The age of onset ranged from 16 to 54 years (mean 34.8 years). The mean values for males and females were 38.7 and 34.1 years respec-

tively. Patients with either paternal or maternal transmission showed no statistical difference in the age of onset of HD (mean 36.9 vs 38.5 years,  $p = 0.73$ ). The duration of illness from onset to death ranged from one to 14 years (mean 8.2 years) with the age of death ranging from 29 to 60 years (mean 43.0 years). Of the 73 patients whose clinical details were available, all exhibited progressive chorea and cognitive impairment and 21 (29%) presented initially with psychiatric symptoms. Four patients of juvenile onset type (age of onset ranging from four to ten) were also reported.<sup>15 29 30</sup> This constituted 4.5% of the total 89 index patients. Three of the four juvenile patients presented with akinetic rigidity and two were a monozygotic twin pair concordant for HD. All four had paternal transmission. Chromosomal abnormality of parallel translocation between chromosome number 2 and 21 was reported in a brother-sister pair both with the disease, with unknown significance.<sup>27</sup> Cognitive assessment,<sup>28</sup> EEG and CT,<sup>15 20 26 27 29</sup> necropsy<sup>15 19 20 26</sup> and treatment response, showed similar findings to those in the West.

Of the 62 HD families whose ancestral origin could be traced, 45 (73%) and 17 (27%) families came from coastal and non-coastal

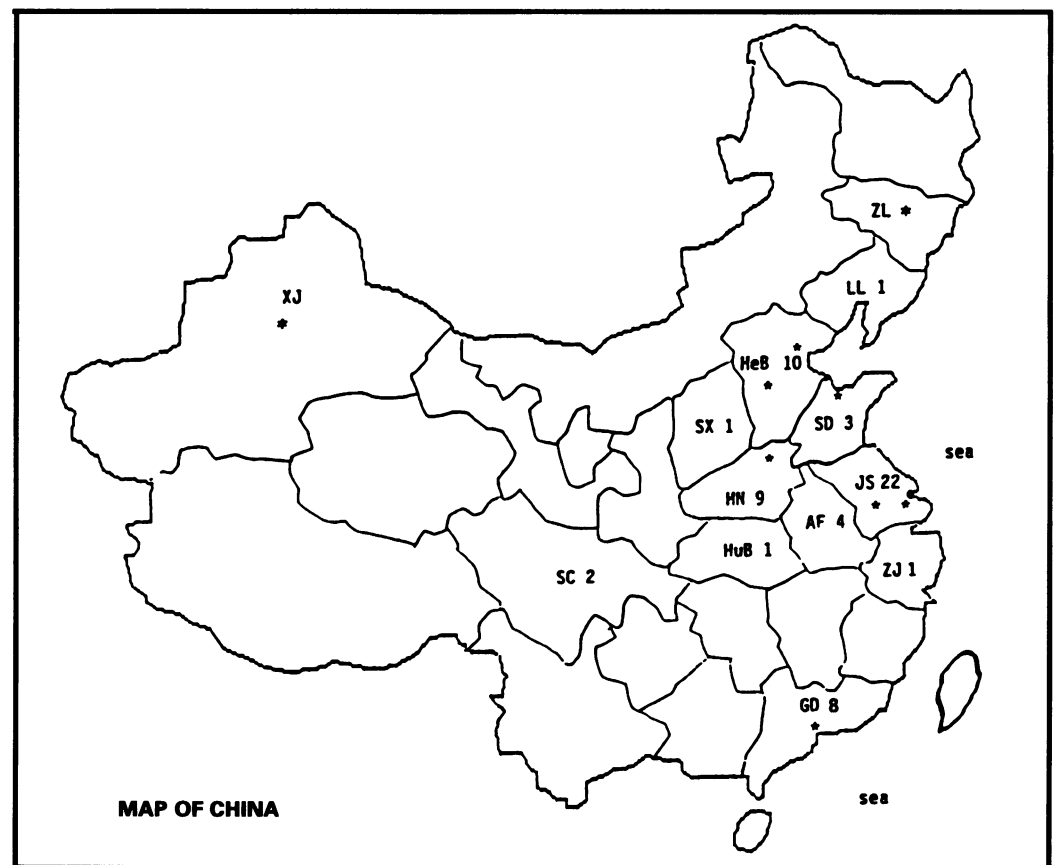


Figure  
\* = reporting centre; XJ = Xinjiang; ZL = Zilin province

Coastal province	Number of cases	Non-coastal province	Number of cases
GD Guangdong	8	AF ANFEI	4
HeB Hebei	10	HN Henan	9
JS Jiangsu	22	HuB Hubei	1
LL Liaoning	1	SX Shanxi	1
SD Shandong	3	SC Sichuan	2
ZJ Zhejiang	1		
Subtotal	45 (73%)	Subtotal	17 (27%)

provinces respectively (figure). Most of them clustered at the coastal provinces of Jiangsu (35%), Hebei (16%) and Guangdong (13%). Two inland provinces, Henan and Anfei, which also reported a fair number of cases, are located just adjacent to Jiangsu and Hebei. The location of reporting centres more or less overlapped with the origin of patients reported (figure), but one family reported from Xinjiang near the western border of China were originally from Jiangsu.

### Discussion

The lack of systematic survey of HD in Mainland China precludes precise estimation of its prevalence. This study in Hong Kong Chinese shows that the period prevalence (1984–91) of the disease was 3.7 per 10<sup>6</sup> and the point prevalence at 1991 was 2.5 per 10<sup>6</sup>, figures that approximate that reported in Japan.<sup>9</sup> Since our study is not a door-to-door population survey, our prevalence data are probably a reasonable though not a full estimate.

The mode of inheritance was invariably autosomal dominant although positive family history could not be obtained in 19%. Since new mutation is rare (less than 0.1%) and penetrance high in HD,<sup>32</sup> the lack of positive family history could best be explained by illegitimacy, denial of the illness, or the chorea in the parents was mild and escaped detection. Internal migration due to war and natural disasters certainly made case-tracing more difficult. An interesting feature in Chinese HD patients, which differs from western findings, was the male predominance both in sex distribution and disease transmission. Paternal transmission was found in two thirds of our patients who had positive history. One possible explanation is sampling bias against the female sex who have a lower social status in the Chinese society, thus attracting less social and medical attention.

The mean age of onset (34.8 years) and age of death (43.0 years) were significantly younger, and the mean duration of illness (8.2 years) were shorter than figures in the West.<sup>4, 34–37</sup> Difference in defining the onset of illness, the standard of medical care and the variation of virulence in different ethnic groups are possible explanations. The favourable influence of maternal factors in the onset of HD<sup>33, 38</sup> was not borne out in our current study, as HD patients with either paternal or maternal transmission showed no difference in the age of onset.

The concentration of cases in the coastal region of China, namely the Jiangsu and Hebei Provinces, is an interesting phenomenon. One explanation may be that these are the more prosperous areas with better medical service and thus a better chance of case discovery and reporting. However, other equally rich but non-coastal provinces, for example, Sichuan, have reported much fewer cases. Furthermore, the Jiangsu family reported in Xinjiang at the western border of China could be more than a coincidence.

This peculiar geographical distribution leads us to postulate that HD in Chinese is not indigenous but has a European origin. In Hong Kong<sup>31</sup> and Taiwan,<sup>39</sup> the oldest families that could be traced were five and four generations respectively. If 25 years is taken as one generation for procreation, the oldest case was probably born in the mid 1800s, when China was invaded by the West. The treaty of Nanking was signed in 1841 with the West gaining access to five ports, including Shanghai in Jiangsu Province,<sup>40</sup> where the Chinese HD patients are concentrated. This date paralleled the arrival of the first HD patients at Tasmania and Venezuela. In contrast to countries like the United States and Venezuela, the disease in China has remained relatively localised in coastal regions. The "ultra-stable" infrastructure of the Chinese culture, hostility of the inland population towards Westerners, and young age of onset and death of Chinese HD patients would help limit extensive spread of the disease.

Racial admixture with white populations may explain the origin of HD in Japanese whose situation is analogous to the Chinese. They traded with the Dutch in the Edo era starting in mid 17th century and other Westerners since the Meiji era in the 19th century. In areas with more foreign contacts, for example, Aichi Province, there is a higher prevalence of HD than neighbouring areas.<sup>8</sup> The Japanese HD gene has recently been found to be similar to its white counterparts in DNA marker studies.<sup>41</sup> This preliminary analysis of Chinese HD patients provides *primi facie* evidence for our hypothesis. To substantiate it, further family tracing and genetic studies including human leucocyte antigen profiles and DNA analysis are required and currently in progress. Should the case be proven, further insight into this rare but tragic disease may be gained.

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